Treatments for Noncutaneous Melanoma

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KEYWORDS

• Uveal melanoma • Ocular melanoma • Mucosal melanoma • Anorectal melanoma • Vulvovaginal melanoma

KEY POINTS

- Molecular characterization of uncommon subsets of melanoma has revealed that mucosal and ocular melanomas are distinct disease subtypes with unique biologic features that have a direct bearing on treatment.
- Surgery, if feasible, offers the best chance for cure in localized ocular and mucosal melanoma. However, in select patients with ocular melanoma, plaque therapy can substitute for enucleation, with similar outcomes.
- Although systemic treatment of advanced disease has historically been guided by the experience with cutaneous melanoma, targeted treatments addressing the unique genetics of ocular and cutaneous melanomas are showing significant promise.

INTRODUCTION

Biology and Epidemiology

Recent advances in the understanding of melanoma have allowed clinicians to move away from a classification system organized according to histologic differences toward a genetics-based system that has important therapeutic and prognostic implications.[1] One consequence of this is that clinicians are now better equipped to understand and exploit the unique characteristics of melanomas that do not arise from the skin.

The number of cases of skin melanoma in the United States in 2013 was estimated to be 76,690.[2] Among melanomas, 5% to 10% are noncutaneous. Such malignancies can be broadly separated into those arising from the eye and those arising from the mucosal surfaces of the body.

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Mucosal melanoma

Approximately 55% of mucosal melanomas (MMs) arise from the head and neck while 24% and 18% arise from the anorectal and vulvovaginal regions, respectively. Melanomas arising from the urinary tract, cervix, esophagus, and gallbladder constitute the remaining 3%.[3]

The epidemiology of MM differs significantly from that of cutaneous melanoma.[3] The median age at diagnosis for MM is 67 years, approximately 1 decade later than for cutaneous disease. Because of the mucosal area associated with the female genital tract, women are approximately 80% more likely than men to be diagnosed with MM, whereas cutaneous melanoma has a slight male predominance. The incidence of MM has remained stable, whereas cutaneous melanomas are being diagnosed with increasing frequency[3]; moreover, unlike the association between exposure to ultraviolet light and fair skin with cutaneous melanoma, there is no well-established risk factor or race predilection for MM.

Prognostically MM is also unique. Irrespective of stage, the 5-year overall survival of MM is 25%, in stark contrast to the 80% survival at 5 years for cutaneous melanoma. Suggested explanations for poor outcomes with mucosal disease include the challenge of diagnosing MM early in its evolution, and the rich lymphovascular supply at mucosal surfaces. Among the subtypes, vulvovaginal disease has the bleakest prognosis, with only 11.4% surviving at 5 years.[3] 19.8% of patients with anorectal MM and 31.7% of patients with head and neck MM are alive at 5 years.[3] There is no universal staging system for MM, as prognosticators remain elusive. Depending on subtype, nodal involvement and size greater than 3 cm appear to correlate with prognosis in retrospective analyses; prospective validation, however, is lacking.[4,5]

Approximately half of all melanomas harbor mutations in BRAF, and only 28% are wild-type for BRAF, NRAS, and KIT. Among MMs, however, 55% are wild-type for these oncogenes. One-quarter of MMs harbor mutations in KIT, 12% have mutations in NRAS, and the remaining 9% contain BRAF mutations.[1,6] The therapeutic implications of these findings are discussed later in this article.

Ocular melanoma

Approximately 95% of ocular melanomas arise from the uvea, including the iris, the ciliary body, and the choroid. Less than 5% arise from the conjunctiva, and less than 1% arise from the eyelid or the orbit. Five percent of all melanomas are ocular, yet most primary ocular cancers in adults are melanomas. Uveal melanoma accounts for 70% of all malignancies arising from the eye.[7]

Approximately 1500 cases of ocular melanoma are diagnosed in the United States annually,[8–10] and cases occur 30% more frequently in men than in women. Independent risk factors for uveal melanoma are light eye or skin color,[11] nevi of the skin or iris,[12] and possibly exposure to ultraviolet light, including occupational exposures (eg, welding).[13]

Although only 1% of patients harbor distant disease at presentation,[14] approximately half of all patients with ocular melanoma succumb to metastatic disease. The precise site of origin has important prognostic implications. Melanomas arising from the iris have a 10-year survival rate of 95%, whereas ciliochoroidal tumors have a 77% survival rate at 10 years after diagnosis. Tumor size, tumor pigmentation, iris color, and degree of local invasion correlate with poor outcomes.[15]

Like MMs, ocular melanomas have unique genetic features that correspond to a distinct biology. GNAQ and GNA11, genes encoding the α subunits of G proteins, are mutated in more than 80% of uveal melanomas, whereas such mutations are present in only 4% of melanomas generally. Such mutations are thought to drive tumor